TRANSFERRING PHARMACEUTICAL BATCH TECHNOLOGY

TO CONTINUOUS FLOW

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The Academic Faculty

By

Olga Yuris Peterson

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TRANSFERRING PHARMACEUTICAL BATCH TECHNOLOGY

TO CONTINUOUS FLOW

Approved by:

Dr. Charles A. Eckert, Advisor
School of Chemical and Biomolecular Engineering
Georgia Institute of Technology

Dr. Charles L. Liotta, Co-Advisor
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. Mark Styczynski
School of Chemical and Biomolecular Engineering
Georgia Institute of Technology

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~ To Mama and Papa ~

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY

The current trend in the pharmaceutical industry is towards continuous flow processes. Continuous flow reactor technology can produce a cheaper, better quality product at reduced energy and environmental cost through more efficient mass and heat transfer. It also enables a simplified and faster approach to bulk production by scaling out as opposed to scaling up. The research presented here focuses on the configuration and installation of a continuous flow system into the laboratory, and the transfer of a Meerwein-Ponndorf-Verley (MPV) reduction from batch to continuous mode.

The Corning® glass continuous flow reactor in our laboratory utilizes specially-designed mixing structures for enhanced mass transfer. Additionally, the glass reactor offers nonreactivity and corrosion resistance over a wide range of temperature and pressure, which conventional steel reactors do not allow. The MPV reduction is a well-known method to prepare primary and secondary alcohols from aldehydes and ketones, respectively. The traditional MPV reduction protocol ($Al(OiPr)_3$ in isopropanol) was modified to enable the technological transfer from batch to continuous mode. This is the first time MPV reduction reactions were carried out in continuous mode. As a result, the MPV reduction of the model compound, benzaldehyde, was successfully conducted with 60% less catalyst and product yield was improved up to 20% (average of 10%) in continuous flow reactions as compared to current batch technology. These results are being used to develop a technology roadmap for the pharmaceutical industry to implement continuous flow processes in their manufacturing operations.

CHAPTER 1

INTRODUCTION

The goal in industry is to produce a lower cost, higher quality product by increasing the overall reaction conversion and selectivity over side-products. [1,2] Continuous flow processes can out-perform conventional batch processes through enhanced mixing and temperature control. [3] In the pharmaceutical industry continuous flow processes are often scaled-out vs. scaled-up to meet an industrial production demand which shortens the product development life cycle. [1] Issues that arise from conventional scale-up such as safety concerns, reaction modification and equipment design, as well as the lengthy delays of pilot plant tests, are avoided by numbering-up in continuous processes.

Enhanced heat transfer in continuous flow reactors is particularly relevant. Overheating of exothermic reactions due to insufficient cooling can lead to substantial side-product formation outside a tight temperature range; and explosive situations. Kockmann and Roberge from Lonza [4] utilized multi-injection principle to transfer a Grignard reaction to continuous mode. They chose phenylethyl magnesium bromide (Grignard) and 2-chloropropionyl chloride (acyl-Cl) for the reaction because this system is very sensitive to side-product formation. They demonstrated that continuous mode multi-injection and good heat transfer reduce hot-spots in the reaction system, increasing the desired product yield from 22% (one continuous flow inlets) to 38% (six continuous flow inlets). They also demonstrated the thermal nature of the reaction, noting that with sufficient cooling, the flow rate has only a small influence on the desired product yield.

The improved thermal control is also important for endothermic reactions, which may shut down due to the lower temperatures caused by insufficient heating. Moreover, if a reaction is equilibrium limited insufficient heat transfer will decrease the equilibrium conversion for both exothermic and endothermic reactions.

Nitration reactions are performed under highly dilute conditions in batch due to the exothermic nature (explosion potential) of organic nitrates, making the process difficult to scale-up in industry. Ducry and Roberge [5] investigated the nitrous acid-catalyzed nitration of phenol. The autocatalytic nature of phenol nitration can result in a thermal runaway scenario. Continuous flow phenol nitration resulted in reduced polymeric side products and up to 20% higher yields when compared to batch reactions (<1 L). The reaction was then intensified, performed virtually solvent-free (10% water to liquefy phenol; and water in the acid). Under these conditions, the polymeric compound formation decreased by a factor of 10 when compared to batch experiments. The best yield of the desired products using the intensified procedure was 77%.

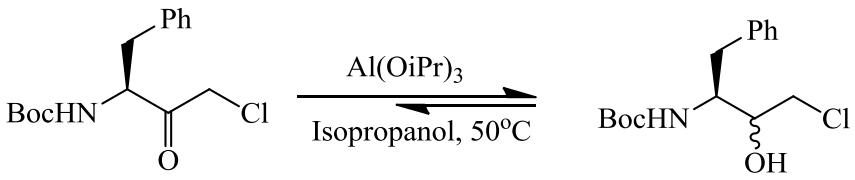
Enhanced mass transfer in continuous flow reactors is particularly relevant for crystallization reactions. Crystal structure and size dictate the properties of the compound. Precise mixing controls the size and size distribution of crystals. Panagiotou *et al*.[6] employed continuous microfluidic reaction technology to produce submicrometer active pharmaceutical intermediate (API) particles. The API was norfloxacin an antibacterial agent, and the solvent/antisolvent system comprised of dimethylsulfoxide and water. Continuous flow experiments resulted in mean particle sizes of 320 nm (60 MPa) to 200 nm (140 MPa). The conventional process (crystallization at low shear followed by repeated microfluidizer processing) resulted in a median particle size of 428

nm (207 MPa). The continuous microfluidic technology resulted in substantially smaller particles and required 23 times less processing, which correlates to shorter processing time and energy efficiency.

The fine chemical and pharmaceutical industries need modular reactors that meet various physico-chemical characteristics (temperature, pressure, and chemical resistance) of synthetic reactions that can be assembled depending on the reaction type being investigated. [1,7] The Corning® glass continuous flow reactor in our laboratory is a modular reactor. It is compatible with a wide range of chemicals and solvents; and corrosion resistant over a wide range of temperature (-60^{o}C to 200^{o}C) and pressure (up to 18 bar). As such, Corning® glass reactors have been used for Grignard reaction[8], hydrogenation[9], autocatalytic nitration[5,10], amidation[11], and precipitation reactions[11].

We investigated the Corning® continuous flow reactor for Meerwein-Ponndorf-Verley (MPV) reduction. The MPV reduction is used a great deal in industry [12, 13] because the reagents are low cost and the reaction is simple and chemoselective.[14, 15] For example, it is employed in the synthesis of HIV protease inhibitors such as Saquinavir®, Amprenavir®, and Atazanavir®. [16, 17, 18] However, a large amount of the conventional catalyst, $Al(OiPr)_3$ is needed to achieve high yields in reasonable time. A key intermediate for HIV protease inhibitors is industrially produces by the batch MPV reduction of N-Boc-(3S)-3-amino-1-chloro-4-phenyl-2 butanone (CMK) at 50^{o}C, 50 mol% $Al(OiPr)_3$ loading, in isopropanol, and a 3 hour reaction time (Figure 1.1). Previous investigations into batch MPV reduction of (S)-CMK in our group developed a new catalyst, $Al(OtBu)_3$ that resulted in a dramatic rate enhancement of the MPV

reduction over the industrial standard $Al(OiPr)_3$ catalyst. The development of the $Al(OtBu)_3$ catalyst enabled the transfer of the batch MPV reaction to continuous mode.



N-Boc-(3S)-3-amino-1-chloro-4-phenyl-2-butanone (**CMK**)

N-Boc-(3S)-3-amino-1-chloro-4-phenyl-2(S,R)-butanol (**CMA**)

Figure 1.1 The MPV reduction of (S)-CMK.

The first step in our investigation was the configuration and installation of a continuous flow system into our laboratory. The Corning® glass reactor was configured with two heat exchangers, two syringe pumps, flow meters, pressure gauges, thermocouples, and pressure relief valves; and tested for leaks (reaction and heat exchanger). The entire system was then installed inside a floor-to-ceiling hood. It is important to note that the entire system is accessible while in the hood. The pumps and heat exchangers can be removed for maintenance and the Corning® reactor can be reconfigured if desired. All the flows of the system (reaction and heat exchanger) were labeled, and system pressure and temperature limits were posted.

The second step was the batch optimization of the MPV reduction of a two model compounds, benzaldehyde (aldehyde) and acetophenone (ketone). The traditional MPV reduction protocol ($Al(OiPr)_3$ in isopropanol) was modified; $Al(OtBu)_3$ catalyst was used because it speeds up the reaction, and a solvent mixture (2:3) of isopropanol and toluene

was used to increase the solubility of $Al(OtBu)_3$. The effect of catalyst (5 and 20 mol%) loading and reaction temperature (65 and 80^oC) on product yield was determined.

The MPV reduction of benzaldehyde was then transferred to the Corning® reactor. The reactor was configured with two feeds: the benzaldehyde dissolved in isopropanol and the catalyst dissolved in toluene. Experimental procedures were developed to ensure reproducibility. Internal standards were added to the stock solutions: dodecane (benzaldehyde solution) and nonane (catalyst solution). System equilibrium experiments were carried out to determine when to start sampling. The effect of catalyst (5 and 20 mol%) loading, reaction temperature (65 and 80^oC), and residence time (2, 4 and 11 min) on product yield was determined.

CHAPTER 2

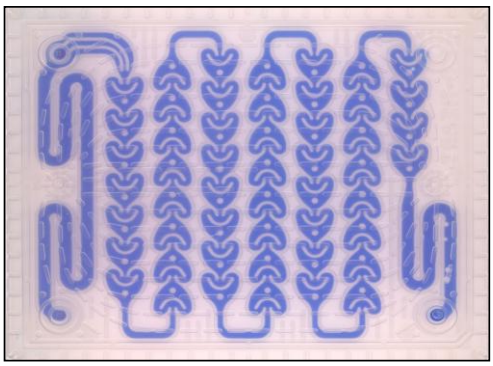
EXPERIMENTAL

2.1 Materials

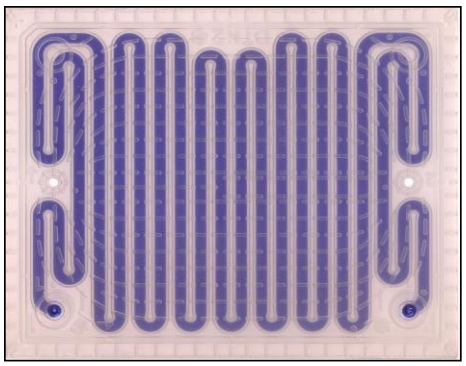
Anhydrous isopropanol, anhydrous toluene, nonane, dodecane, industrial grade $Al(OtBu)_3$, benzaldehyde, benzyl alcohol, and 1-phenylethanol where purchased from Sigma Aldrich and used as received. Reagent grade methanol was purchased from VWR and used as received. Concentrated hydrochloric acid was purchased from VWR and was diluted to 2M. Acetophenone was purchased from Sigma Aldrich and vacuum distilled (99.9% by HPLC).

2.2 Equipment

We are employing a versatile glass continuous flow reactor developed by Corning®. The borosilicate glass construction is compatible with a wide range of chemicals and solvents; and corrosion resistant over a wide range of temperature (-60^{o}C to 200^{o}C) and pressure (up to 18 bar). Corning has specifically engineered mixing reactor modules for heterogeneous systems which optimize mixing. Linear reactor modules are used for heating or cooling and residence time (Figure 2.1). All of the reactor modules are jacketed for enhanced thermal control (-60^{o}C to 200^{o}C, up to 3 bar). As a consequence, these reactor modules facilitate an optimum surface-to-volume ratio for improved heat transfer.



Mixing Module



Linear Module

Figure 2.1 The mixing and linear reactor modules of the Corning® glass reactor.

The Corning® continuous flow glass reactor in our laboratory is modular. It is made of nine reactor modules (5 mixing and 4 linear), three temperature regions and six possible inlets. The reactor is versatile, enabling multistep synthesis including: reagent pre-heating, pre-cooling and reaction quenching.

Our system (Figure 2.2), which includes two ISCO 500D Syringe Pumps and two heat exchangers (a LAUDA Integral XT150 and a Thermo Election Corp. NESLAB RTE7), is housed in a floor-to-ceiling hood in our laboratory (Figure 2.3). Pump flow rates are monitored using flow meters (Omega, PTFE construction and sapphire float). The system pressure is measured using pressure gauges (Matheson, 316 stainless steel, 0-30psig) and both inlets to the reactor have pressure relief valves (Swaglok, 316 stainless steel).

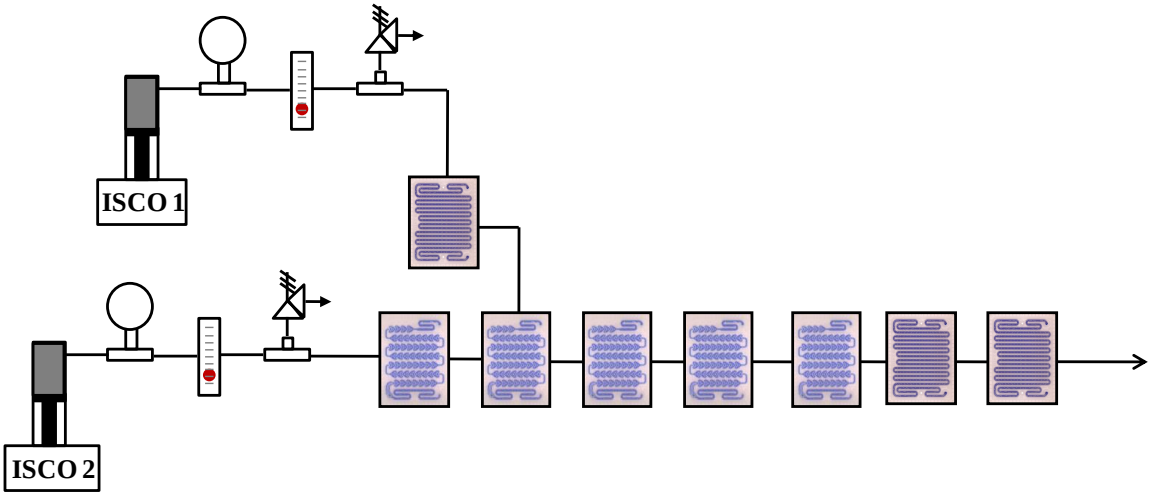


Figure 2.2 The 8 module configuration of the continuous flow system.

Figure 2.3 The hood installation of the entire continuous flow system.

The batch experiments were carried out in a Radleys Carousel 12 Reaction Station to ensure consistent reaction conditions (Figure 2.4). The carousel design allows for

simultaneous heating, stirring and refluxing of 12 reactions (1 to 20 mL total volume) under inert atmosphere. The carousel stirring hotplate has a temperature range from room temperature to 180^{o}C (± 0.1^{o}C) and ensures equal stirring at all 12 positions. The integrated reflux head of the carousel system is controlled by a heat exchanger (Thermo Election Corp., NESLAB RTE7) to reduce solvent evaporation and subsequent loss.

Figure 2.4 Radleys Carousel 12 Reaction Station.

For reaction monitoring and analysis an Agilent Series 1100 LC with UV-vis detector was used. A Luna 5µ, C18 column was used and the HPLC solvents are acetonitrile and water (0.1 vol% trifluoroacetic acid in water). For continuous flow experiments, the internal standards nonane and dodecane were analyzed using an Agilent 6890 series GC with FID detector. A HP-5 column 30m x 0.25 mm and 0.25 µm was used and helium was the carrier gas.

2.3 Experimental Methods

All continuous flow reactions were performed using the continuous flow system in Figure 2.3. Stock solutions of the reagents were prepared under anhydrous conditions.

A 0.75 mmol/mL solution of benzaldehyde in isopropanol was made and 1.0 vol% dodecane was added to the solution to make the final stock solution. For 20 mol% catalyst loading experiments, a 0.11 mmol/mL solution of $Al(OtBu)_3$ in toluene was made and 1.0 vol% nonane was add to the solution to make the final stock solution. For 5 mol% catalyst loading experiments, a 0.03mmol/mL solution of $Al(OtBu)_3$ in toluene was made and 1.0 vol% nonane was add to the solution to make the final stock solution. The hydrocarbons dodecane and nonane act as internal standards; they do not participate in the reaction. Solids were weighed out using a balance (Mettler Toledo, AT21 DeltaRage ®, ± 0.001g). Liquid compounds were measured using NORM-JECT luer lock syringes and Eppendorf research pipettes.

From Figure 2.2, ISCO 2 delivers the catalyst in toluene and ISCO 1 delivers the substrate in alcohol. Before initializing the flow experiments, the piston pumps were loaded with the reagent and catalyst stock solutions. A filter (Swagelok, 140 micron) was used when loading the catalyst stock solution. The ISCO reservoirs do not have mixing, so before each flow rate experiment a "0 sample" of the reagent solutions was collected after the flow meter to account for any concentration gradient in the reservoir. The ISCO pumps continuously delivered the stock solutions to the Corning® reactor at a 2:3 volume ratio of reagent to catalyst. The system was allowed to equilibrate for two reactor volumes at the set flow rate before collecting samples. After equilibrium, three reaction samples were collected, one reactor volume apart, and averaged to calculate experimental error.

For organic content analysis, 1.0 mL of the collected reaction sample was cooled in an ice bath, quenched with 0.4 mL of 2M HCl for 5min and then diluted with 16 mL of

methanol. The quenched reaction solutions were then diluted 10:1 for HPLC analysis. This dilution was repeated twice. The disappearance of starting material and appearance of product was quantified using calibration curves as follow: benzaldehyde at 254λ and 2.64 min, R^2= 0.999; benzyl alcohol at 210λ and 1.73 min, R^2 = 0.999; acetophenone at 210λ and 2.72 min, R^2 = 0.994; and 1-phenylethanol at 210λ and 2.03 min, R^2 = 0.987. Figure 2.5 shows the calibration curves that were used.

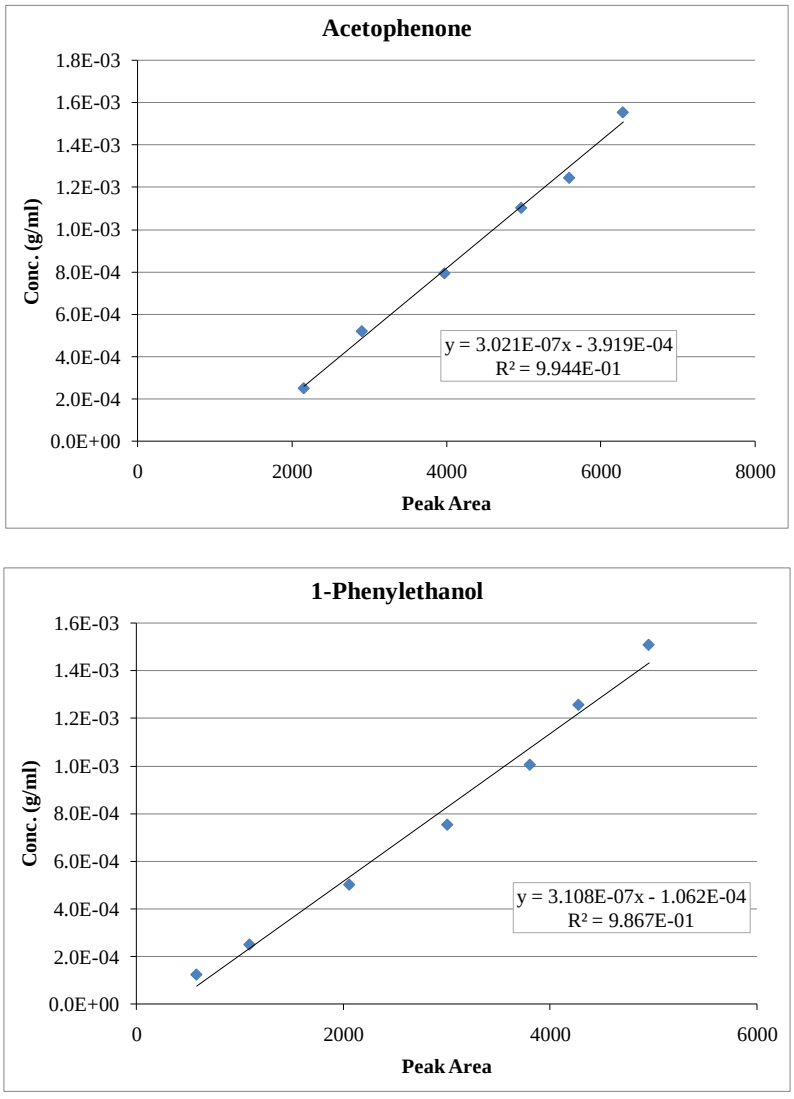
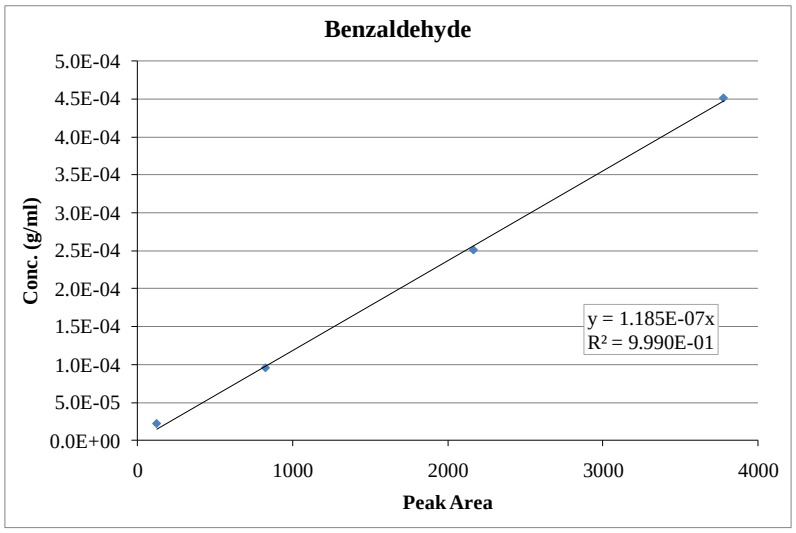


Figure 2.5 HPLC calibration curves for the MPV reaction reagents and products.



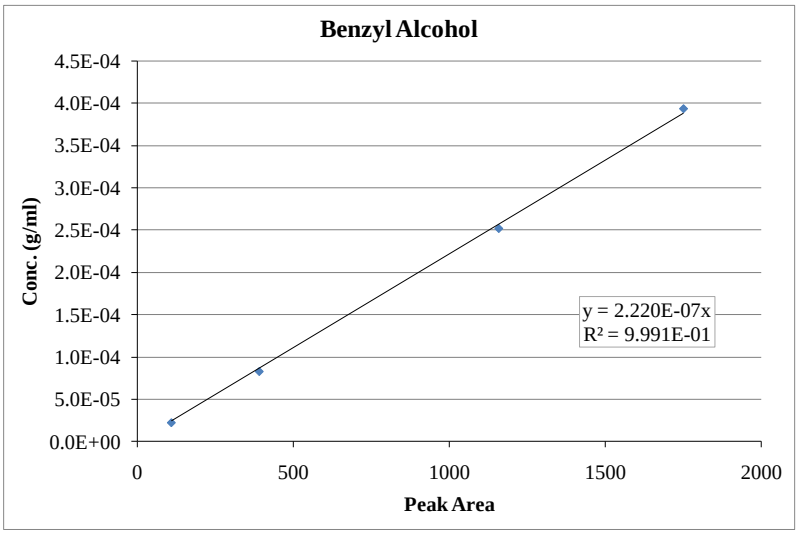


Figure 2.5 Continued.

The internal standards, nonane and dodecane were monitored by GC from a 1.0 mL sample collected from reaction (nonane at 2.9 min, dodecane at 7.9 min). The ratio of the internal standard peak area after reaction to that before reaction ("0 samples") allows us to accurately track the volume ratio the two piston pumps are achieving. This ratio was used to calculate the amount of benzaldehyde available for reaction and accurately calculate yield and conversion when combined with the HPLC data.

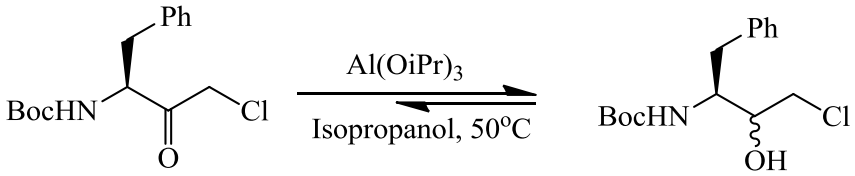
All batch reactions were performed using the Radleys carousel systems in Figure 2.4. Stock solutions of the reagents were prepared under anhydrous conditions. A 0.75mmol/mL stock solution of benzaldehyde in isopropanol was made (0.78 mmol/mL acetophenone). For 20 mol% catalyst loading experiments, a 0.11 mmol/mL stock solution of $Al(OtBu)_3$ in toluene was made (0.11 mmol/mL $Al(OtBu)_3$ for acetophenone experiments). For 5 mol% catalyst loading experiments, a 0.03 mmol/mL solution of $Al(OtBu)_3$ in toluene was made. The batch reactions all had a total reaction volume of 5 mL and a 2:3 volume ratio of reagent to catalyst. To stop the reaction, the entire reaction volume was cooled in an ice bath and then quenched with 2mL of 2M HCl for 5 min, before being diluted with 30mL of methanol. The quenched reaction solution was then diluted 10:1 for HPLC analysis. The organic content was quantified using the calibration curves in Figure 2.5.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Meerwein-Pondorf-Verley (MPV) Reduction Reaction

The MPV reduction reaction is widely used in industry [14, 15] because the reagents, $Al(OiPr)_3$ and isopropanol, are low cost and the reaction is chemoselective.[9, 10] For example, it is employed in the synthesis of HIV protease inhibitors such as Saqqinavir®, Amprenavir®, and Atazanavir®. [6, 12, 13] A key intermediate for these HIV protease inhibitors is produced on an industrial scale by the batch MPV reduction of N-Boc-(3S)-3-amino-1-chloro-4-phenyl-2 butanone (CMK) at 50°C, 50 mol% $Al(OiPr)_3$ loading, in isopropanol, and 3 hour (Figure 3.1).



N-Boc-(3S)-3-amino-1-chloro-4-phenyl-2-butanone (**CMK**)

N-Boc-(3S)-3-amino-1-chloro-4-phenyl-2(S,R)-butanol (**CMA**)

Figure 3.1 The MPV reduction of (S)-CMK to (S,R) and (S,S)-CMA.

Previous research in our group into the MPV reduction of CMK, resulted in the discovery that the rate of reduction is drastically increased when $Al(OtBu)_3$ replaces the traditional $Al(OiPr)_3$ catalyst (Figure 3.2). The MPV reaction catalyzed by $Al(OtBu)_3$ is complete after 15 min, while the analogous $Al(OiPr)_3$ catalyzed reaction reaches completion after 2 hours. Because t-butoxide ligands do not have alpha hydrogen, the

reaction can only take place upon ligand exchange with isopropanol. However, the rate enhancement is attributed to the difference in aggregation state between the $Al(OtBu)_3$ (dimeric) versus the $Al(OiPr)_3$, which is tetrameric. The reactions were also conducted in a 9:1 toluene/isopropanol solvent mixture (Figure 3.3). Again, the $Al(OtBu)_3$ catalyzed reactions showed higher activity than $Al(OiPr)_3$, but as expected due to dilution effect, the MPV reduction in toluene required about twice as long to achieve the same product yield as the reaction in pure isopropanol.

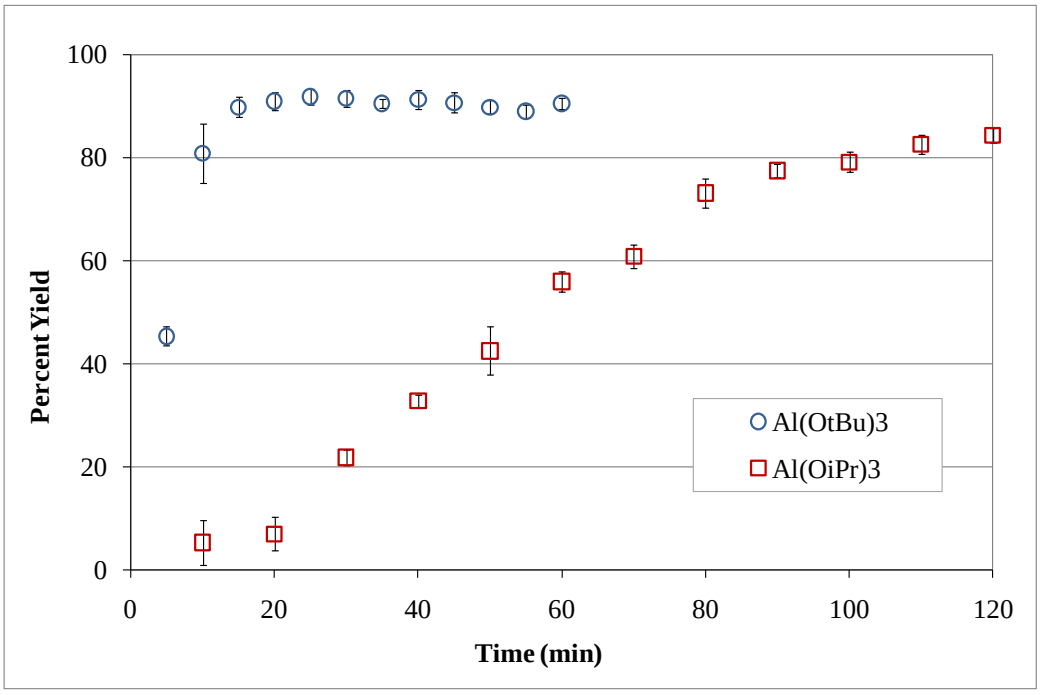


Figure 3.2 The MPV reduction of (S)-CMK using $Al(OtBu)_3$ and $Al(OiPr)_3$.

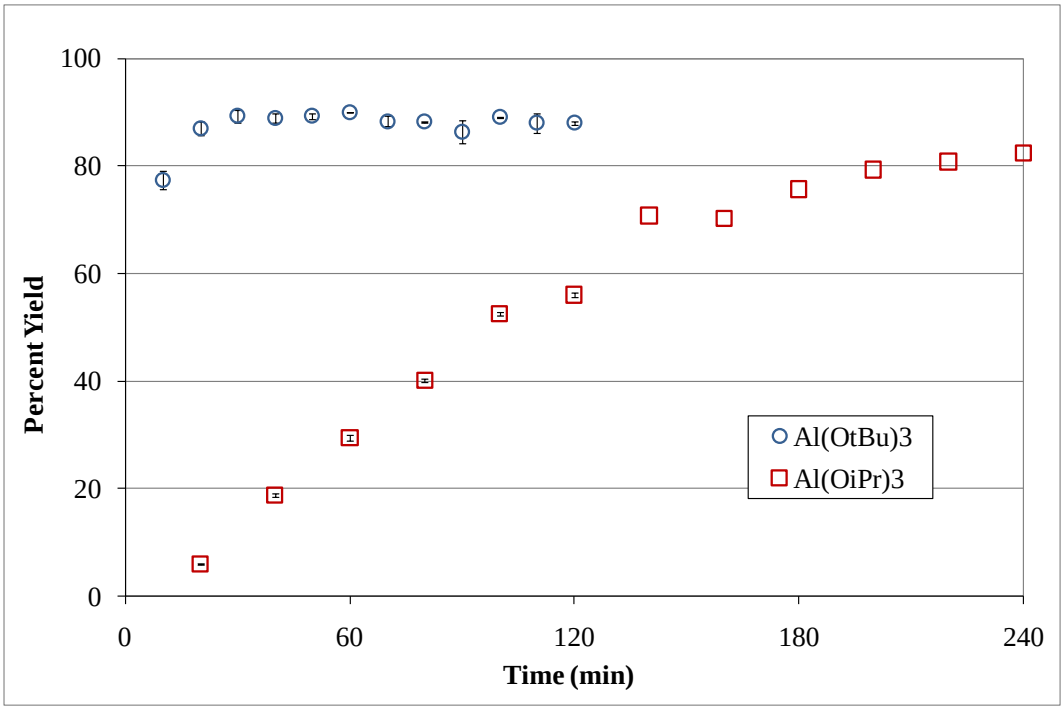


Figure 3.3 **The MPV reduction of (S)-CMK in a 9:1 toluene/isopropanol solvent mixture using $Al(OtBu)_3$ and $Al(OiPr)_3$.**

The rate enhancement allowed for the amount of catalyst to be reduced for the reaction to take place on the same time scale as the $Al(OiPr)_3$. Catalyst loading was investigated in the MPV reduction of (S)-CMK on a 5 mL reaction scale in a carousel reactor. 50, 40, 30, 20, 10, and 5 mol % were compared using $Al(OtBu)_3$ in isopropanol at 50^{o}C (Figure 3.4). Catalyst loadings from 50 to 20mol% show similar reaction rates. At the lower loadings of 10 and 5 mol%, the rates became significantly lower.

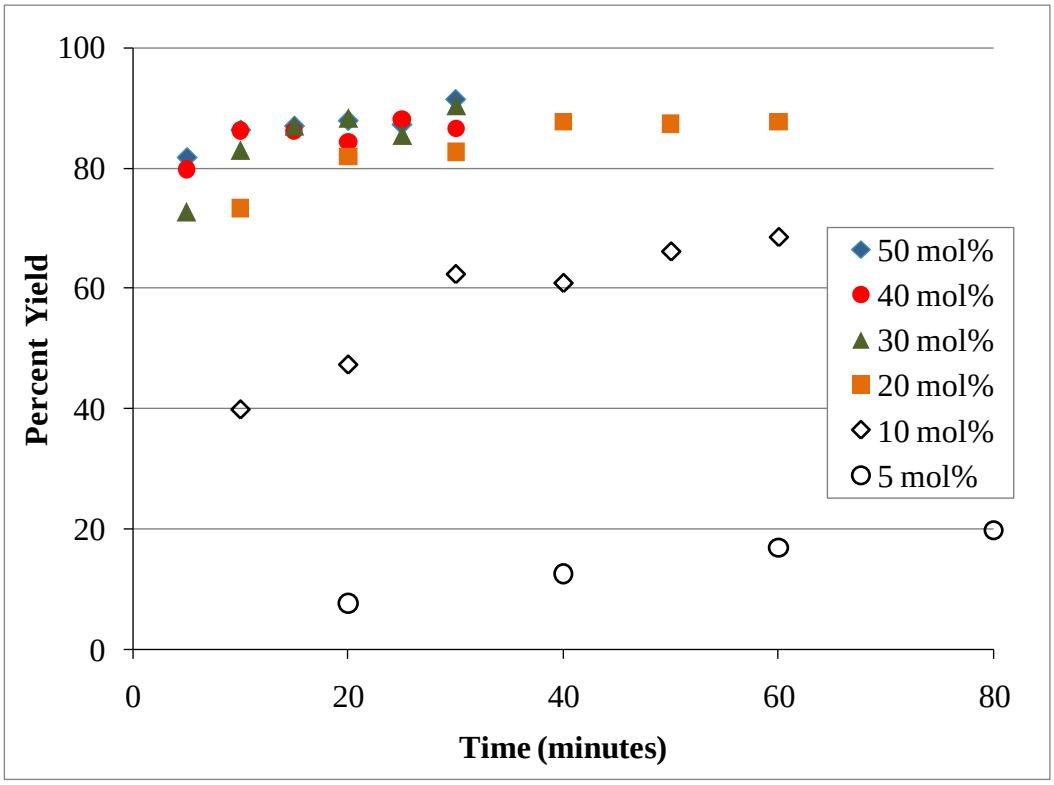


Figure 3.4 **The MPV reduction of (S)-CMK at various $Al(OtBu)_3$ loadings.**

3.2 Batch MPV Reduction Reactions

3.2.1 Benzaldehyde

The traditional MPV reduction protocol ($Al(OiPr)_3$ in isopropanol) was modified to enable the technological transfer from batch to continuous mode. All batch and continuous mode reactions discussed here used $Al(OtBu)_3$ and a 3:2 volume ratio of toluene to isopropanol. The $Al(OtBu)_3$ increased the rate of reaction and the solvent mixture increased the solubility of the catalyst. The MPV reduction of the model compound benzaldehyde (Figure 3.5) was investigated at two catalyst loadings (20 and 5 mol%) and two reaction temperatures (65 and 80^{o}C). At 20 mol% and 80^{o}C, the reaction is complete after 12 min; therefore increasing the temperature by 15^{o}C increased the

product yield by an average 25% (Figure 3.6). At 5 mol% catalyst loading, increasing the temperature by 15°C increased the product yield by an average 15% (Figure 3.7). The 5 mol% reactions do not go to completion as seen in Figure 3.7. This may be due to any inherent moisture in the system causing the hydrolysis of the $Al(OtBu)_3$. But, at an order of magnitude lower catalyst loading than the industrial protocol, the reaction reached 80% yield in 35 min.

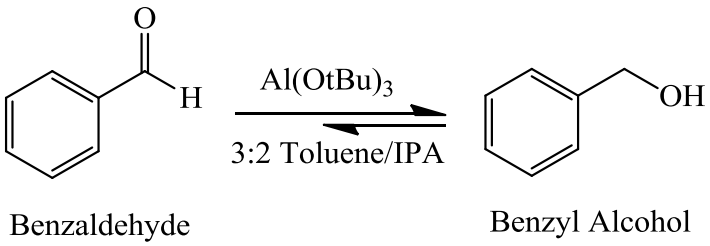


Figure 3.5 The modified MPV reduction for benzaldehyde.

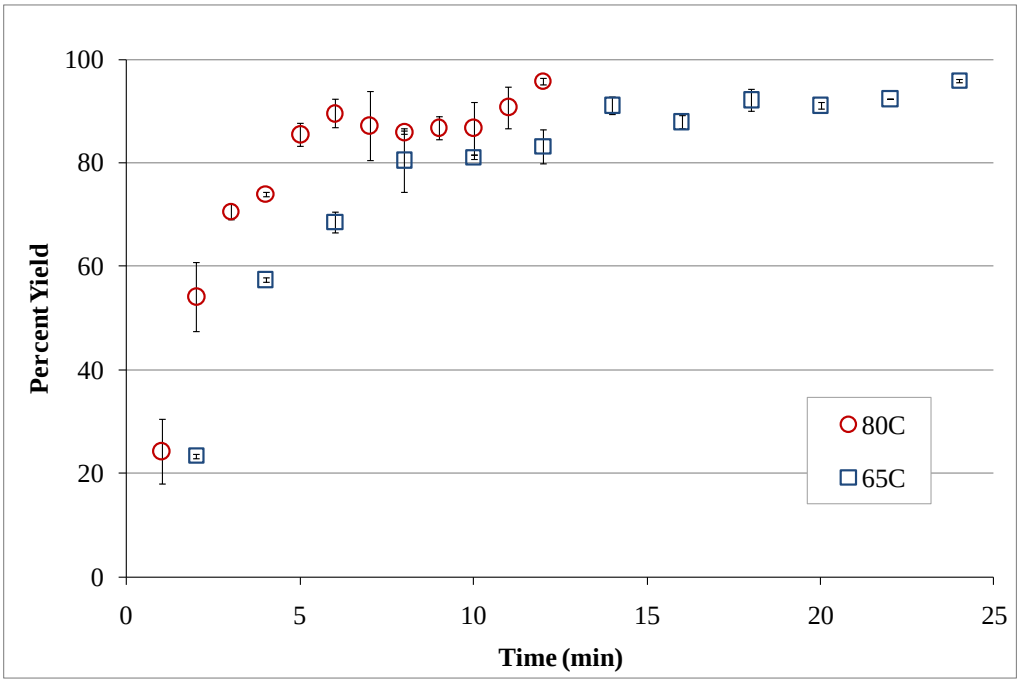


Figure 3.6 Batch MPV reduction of benzaldehyde: 20 mol%, 80°C and 65°C.

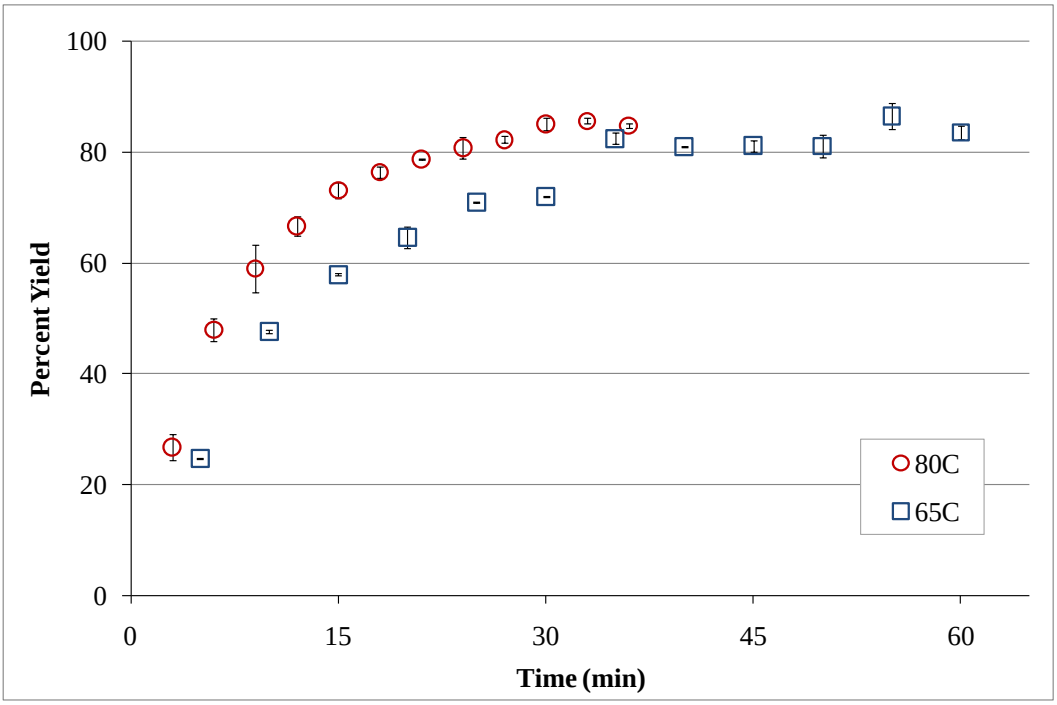


Figure 3.7 **Batch MPV reduction of benzaldehyde: 5 mol%, 80°C and 65°C.**

A pseudo 1st order kinetic analysis was performed on the batch kinetic data in Figures 3.6 and 3.7 to estimate the apparent rate constant for the MPV reduction of benzaldehyde at the various reaction conditions. The simplified rate of reaction equation (Figure 3.8) and the integral method analysis resulted in Table 3.1. Increasing the reaction temperature by 15°C (keeping all other reaction conditions the same), increases the apparent rate constant two fold, whereas increasing the catalyst loading by 15 mol%, increases the apparent rate constant almost five fold.

$$-r_{BA} = -\left(\frac{dC_{BA}}{dt}\right) = k_{app} * C_{BA}$$

$$\boldsymbol{k_{app}} = \text{Apparent Rate Constant}$$

Figure 3.8 **The simplified rate of reaction for the MPV reduction of benzaldehyde.**

Table 3.1 Pseudo 1st order estimate apparent rate constants for MPV reactions.

Reaction Temp. (^oC)	$Al(OtBu)_3$ Loading (mol%)	Average k_{app} (min^{-1})
65	5	0.033
	20	0.168
80	5	0.077
	20	0.338

3.2.2 Acetophenone

The MPV reduction of the second model compound, acetophenone, was investigated. Because ketones are known to react more slowly under MPV conditions than aldehydes, the investigation was started with the optimized reaction conditions of 20 mol% $Al(OtBu)_3$ and 80^{o}C (Figure 3.9). The MPV reduction of acetophenone reaches 70% yield after one hour (Figure 3.10).

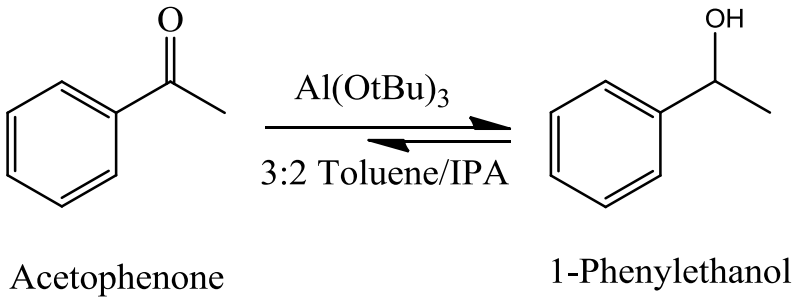


Figure 3.9 The acetophenone MPV reduction scheme.

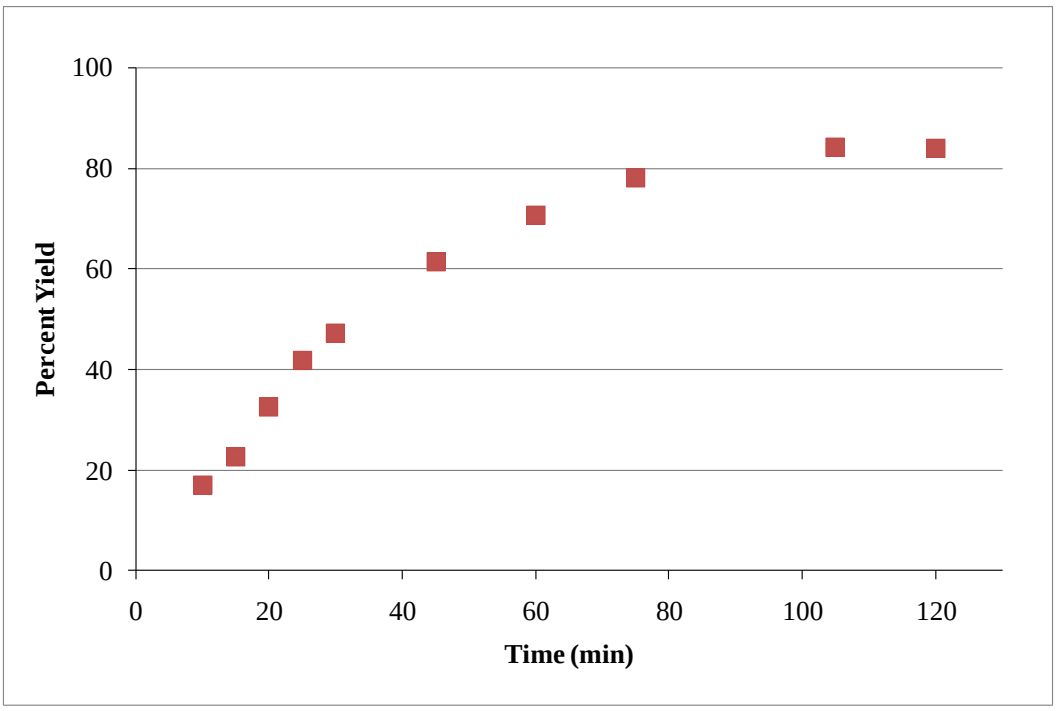


Figure 3.10 Batch MPV reduction of acetophenone at 80°C and 20mol% $Al(OtBu)_3$.

3.3 Continuous Flow Experiments

Two reactor configurations were investigated for the MPV reduction of benzaldehyde. The initial configuration included two mixing modules (reactor volume of 16 mL) (Figure 3.11). Five residence times were investigated; 3, 1, 0.5, 0.27 and 0.18 min, corresponding to total flow rates of 5, 15, 30, 60 and 90 mL/min, at 65°C and 20 mol% $Al(OtBu)_3$ (Figure 3.12). From the results we can see that reducing the total flow rate (increasing residence time), increases yield up to 46% at 3 min (the longest residence time possible with this configuration).

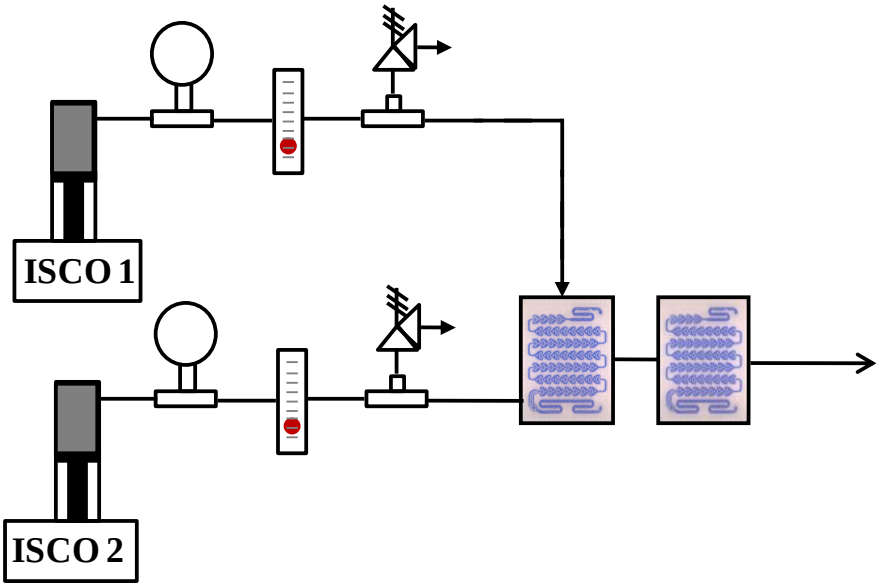


Figure 3.11 **Configuration of the continuous flow system: two mixing modules.**

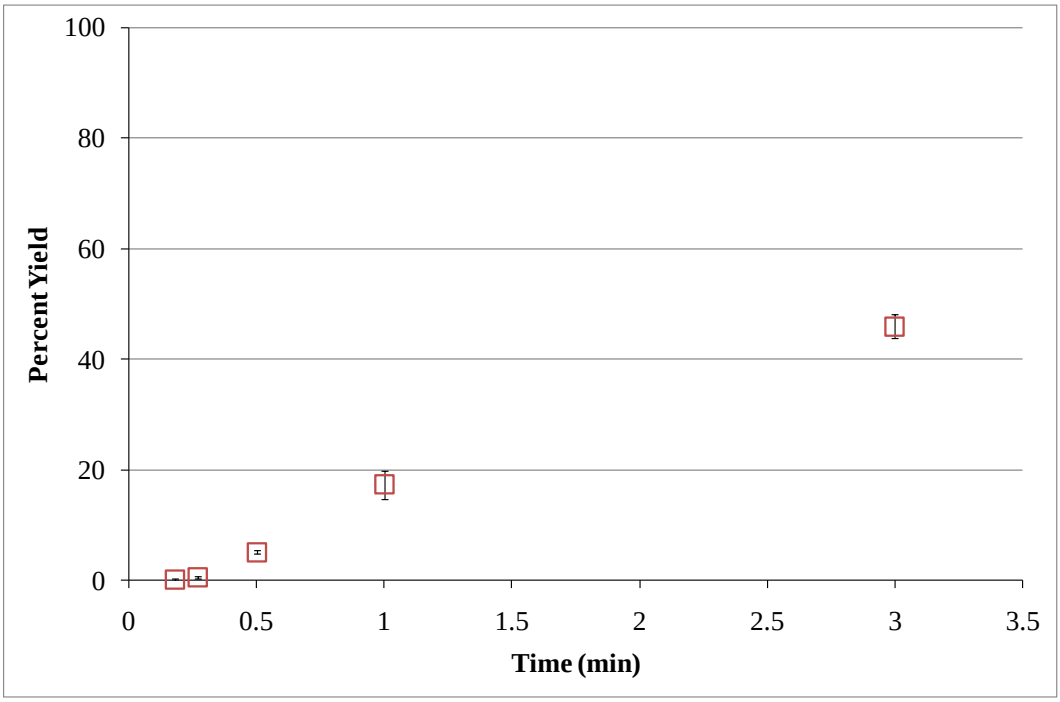


Figure 3.12 **Continuous flow (2 modules) MPV reduction of benzaldehyde: 65°C, 20mol%, 5 residence times (3, 1, 0.5, 0.27 and 0.18 min).**

The final reactor configuration utilizes 8 reactor modules (5 mixing and 3 linear modules), and incorporates preheating of the reagent streams (Figure 3.13). With this configuration, the reactor volume was increased to 48 mL (considering only modules where reaction is occurring). The residence times investigated were 2, 4 and 11 min correspond to flow rates of 30, 15 and 5 mL/min, respectively. Internal standards were introduced to the reagent stock solutions in 1 vol% to accurately measure flow rates. The parameters that were varied were residence time (flow rate), temperature, and catalyst loading.

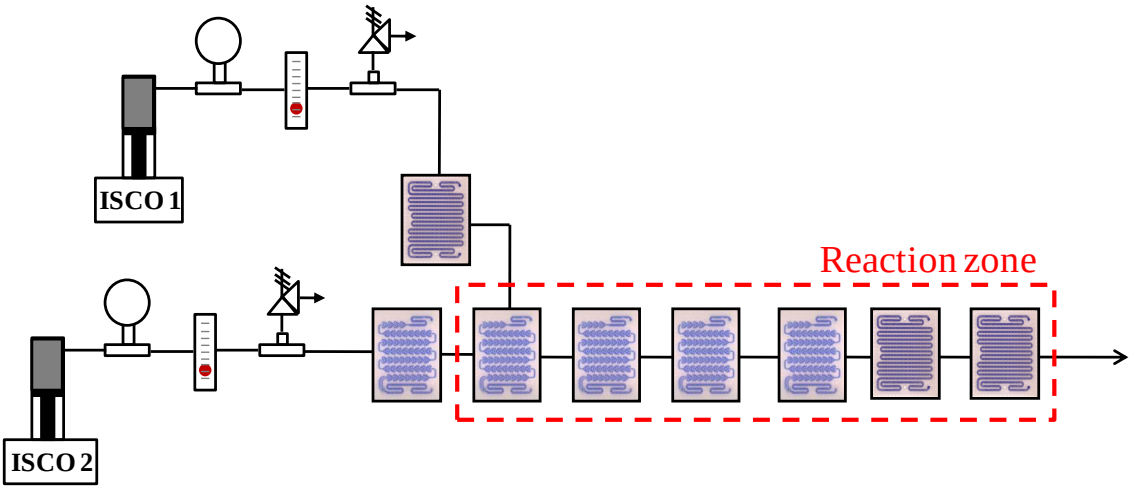


Figure 3.13 Configuration of the continuous flow system: eight modules.

From Figure 3.14, we can see that increasing the residence time and temperature of the reaction increased product yield, from 44% yield (20 mol% $Al(OtBu)_3$, 2min residence time and 65^{o}C) up to 98% yield (at 20 mol% $Al(OtBu)_3$, 11 min residence time and 80^{o}C). When we compare the continuous flow results (red circles) with batch (blue squares), the continuous reactor exhibits a significant yield enhancement at shorter reaction times (Figure 3.15). Specifically, the yield increases by up to 20% at a residence

(reaction) time of 2 min for reaction at 65°C and 80°C. The yield increase observed with the continuous reactor was attributed to enhanced mixing in the continuous flow reactor compared to batch mode.

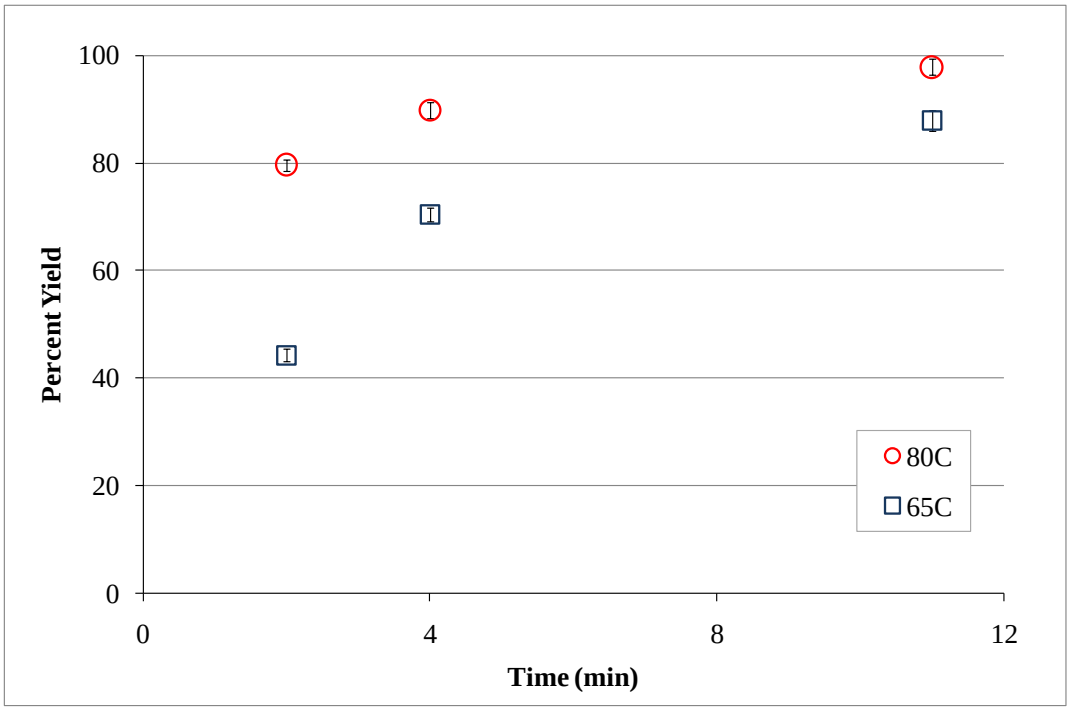
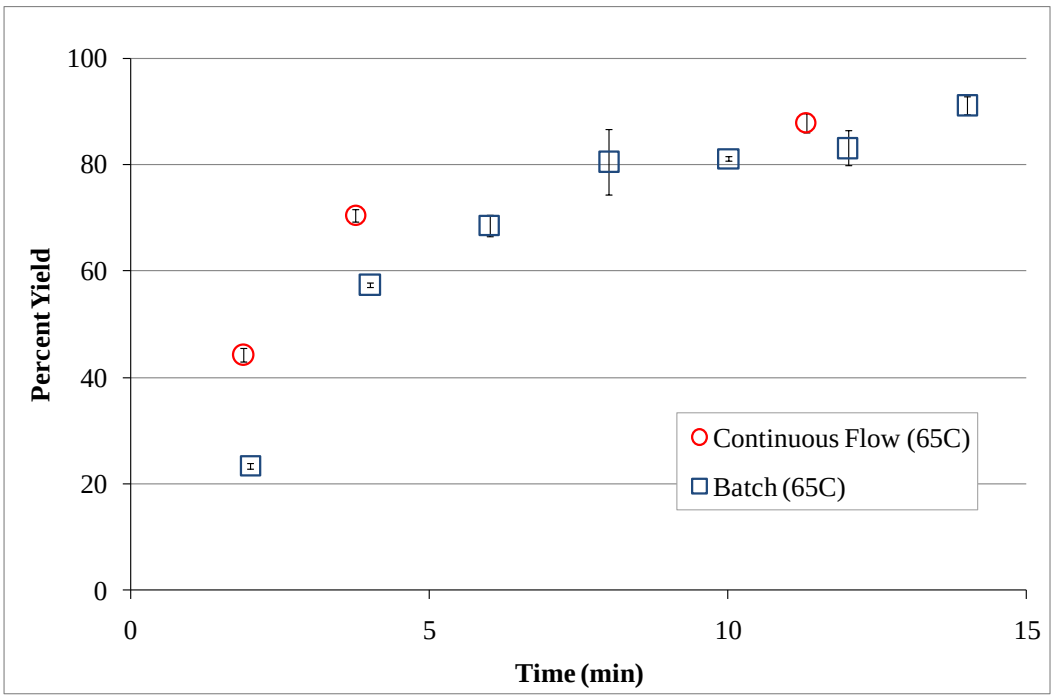


Figure 3.14 **Continuous flow (8 module) MPV reduction of benzaldehyde: 20 mol% $Al(OtBu)_3$, at 65°C and 80°C.**



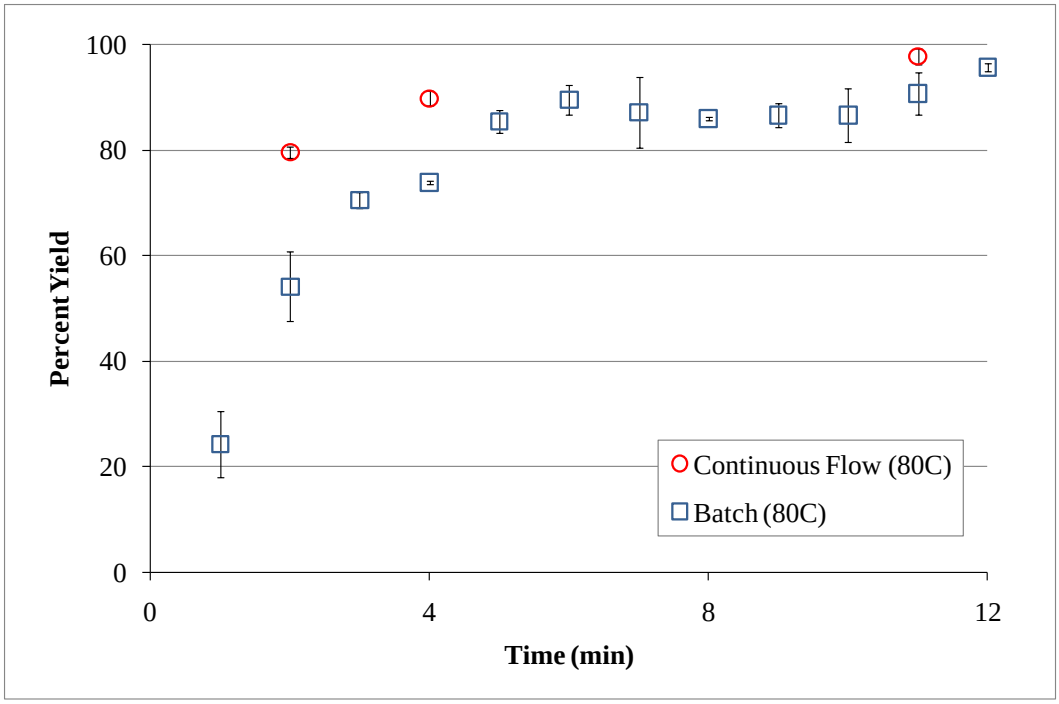


Figure 3.15 Batch and continuous flow MPV reduction of benzaldehyde: 20 mol% $Al(OtBu)_3$, at 65°C and 80°C.

The reduction in catalyst loading to 5 mol % was studied for the MPV reduction of benzaldehyde. A reaction yield of 77% is observed when the MPV reaction is run at

80°C and 11 min residence time (Figure 3.16). When we compare the continuous flow results with batch (identical reaction conditions), we again observe significant yield enhancement (Figure 3.17). The yield increases by up to 10% at the two shortest residence times for reaction at 65°C and 80°C.

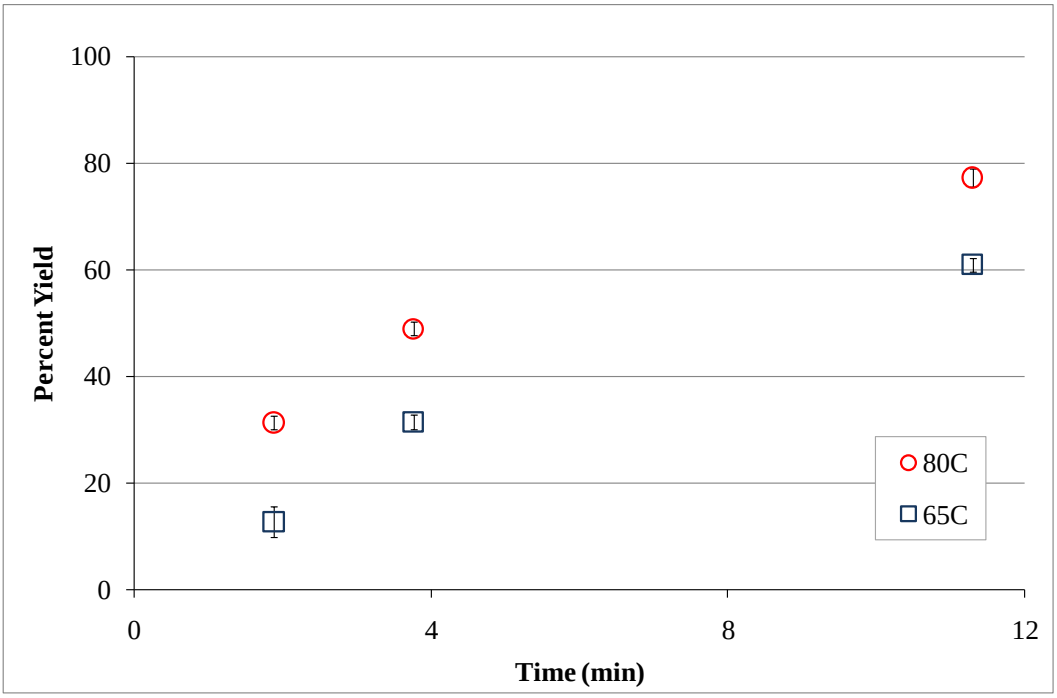
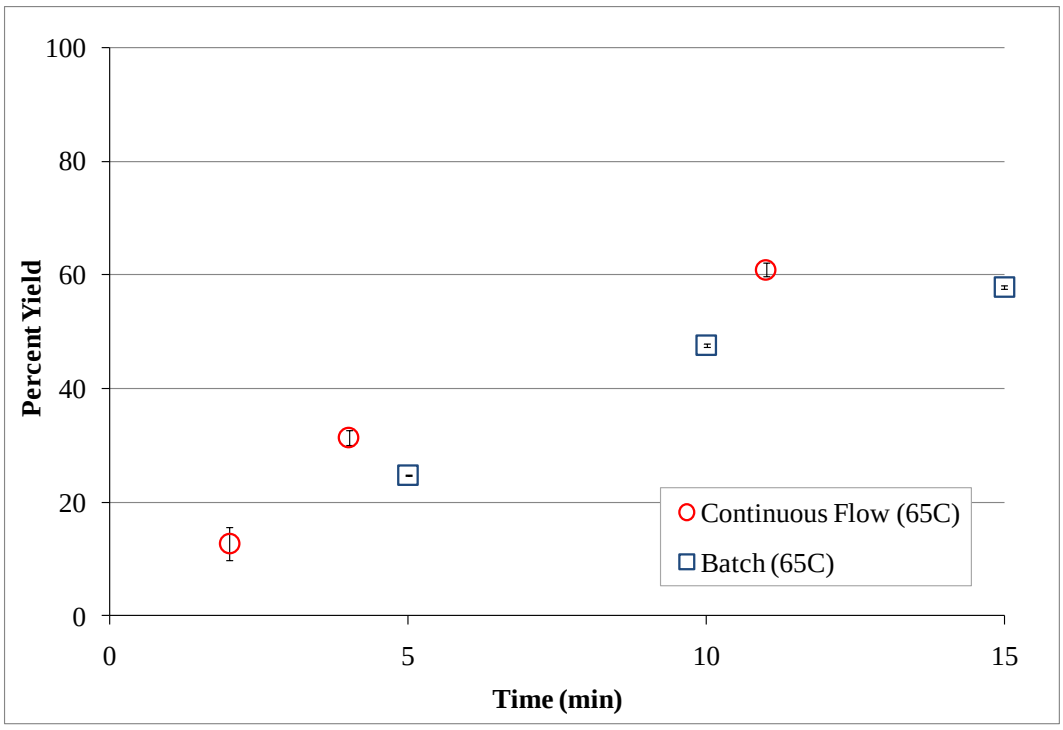


Figure 3.16 **Continuous flow (8 module) MPV reduction of benzaldehyde: 5mol% $Al(OtBu)_3$, at 65°C and 80°C.**



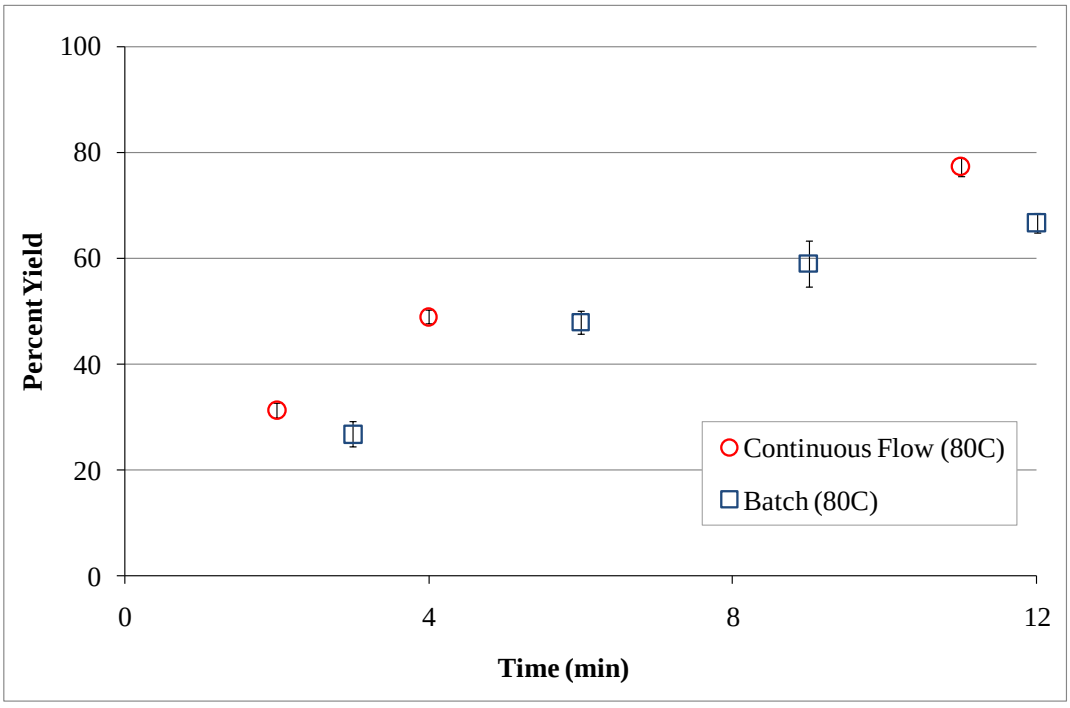


Figure 3.17 **Batch and continuous flow MPV reduction of benzaldehyde: 5 mol% $Al(OtBu)_3$, at 65°C and 80°C.**

CHAPTER 4

CONCLUSIONS

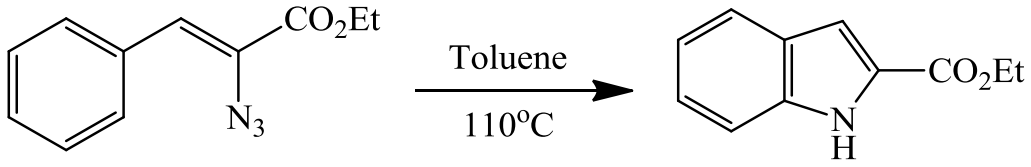
We have configured and installed a Corning® glass continuous flow system into a floor-to-ceiling hood in our laboratory. The hood installation allows for future investigations of high temperature reactions and reactions with hazardous reagents. The system flow and pressure can be monitored during reaction to ensure normal operation and reaction. We have developed experimental procedures for continuous flow reactions by successfully transferring a batch MPV reduction to continuous mode. This is the first time a MPV reduction were carried out in continuous mode. The MPV reduction of the model compound, benzaldehyde, was successfully conducted with 60% less catalyst than in the industrial batch protocol and product yield was improved up to 20% for 20 mol% $Al(OtBu)_3$ continuous flow experiments and up to 10% for 5 mol% $Al(OtBu)_3$ continuous flow experiments as compared to batch experiments. Industrially, this is significant as it means coast savings and a reduction of the metal-contaminated waste stream. These results are being used to develop a technology roadmap for the pharmaceutical industry to implement continuous flow processes in their manufacturing operations.

CHAPTER 5

RECOMMENDATIONS

5.1 Hemetsberger Indolization Reaction

Indole containing compound are important in the pharmaceutical industry because they are precursors for many bioactive molecules. The Hemetsberger reaction involves the slow addition of the azido-precursor solution into refluxing toluene (110^{o}C), inducing the formation of the indole ring via the formation of a reactive nitrene intermediate (Figure 5.1)[19]. The intermediate nitrene in this reaction is highly reactive and decomposes readily and the loss of nitrogen is an exothermic reaction. The Corning® reactor can be a distinct advantage to maintaining a very narrow temperature range and good mixing throughout the experiment to ensure a high yield and reproducibility.



(*Z*)-ethyl 2-azido-3-phenylacrylate Ethyl 1*H*-indole-2-carboxylate

Figure 5.1 Hemetsberger indolization reaction of (Z)-ethyl 2-azido-3-phenylacrylate.

Operating the Corning® continuous flow reactor with multiple inlets (Figure 5.2) mimics the batch Hemetsberger reaction procedures. ISCO 1 delivers toluene which is preheated to 110^{o}C. ISCO 2 and Eldex 1 deliver the reagent dissolved in toluene.

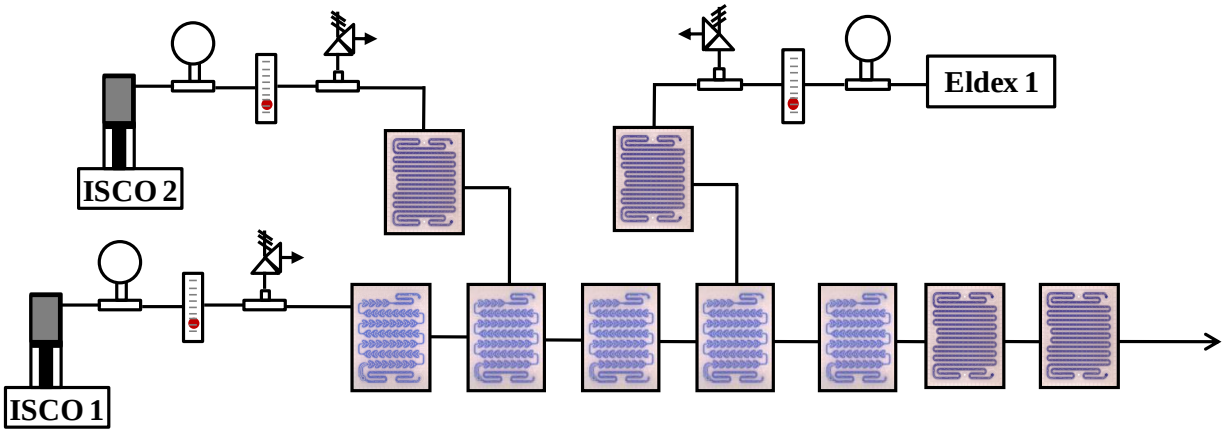


Figure 5.2 The multi-injection continuous flow system configuration.

5.2 Phase Transfer Catalysis

The enhanced mass transfer in the specifically designed Corning® continuous reactor can be taken advantage of by running a liquid-liquid Phase Transfer Catalysis (PTC) reaction (Figure 5.3)[20,21]. PTC is a technique for conducting reactions between reagents that are not miscible with each other. Therefore, the phase transfer catalyst transfers reagent(s) into the reaction phase and the products back out into the supply phase. This approach is widely used to manufacture polymers, pharmaceuticals, agricultural products and petrochemicals. There are multiple benefits to employing PTC reactions: (1) use of benign solvents, (2) lower costs, (3) shorter reaction times and lower reaction temperatures, (4) easy recovery of products, (5) recycling of the system.[22]

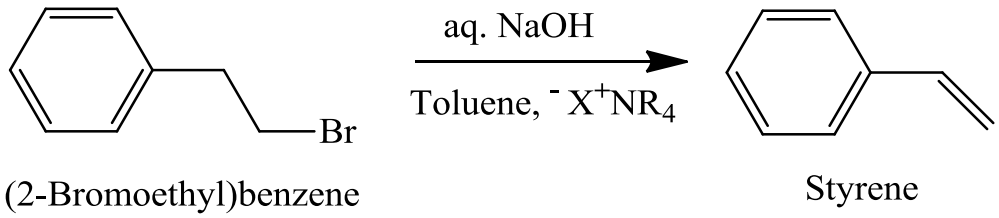


Figure 5.3 PTC elimination reaction of (2-bromoethyl)benzene.

To take advantage of all the specially designed mixing modules of the Corning® reactor, I propose the following configuration (Figure 5.4). ISCO 1 delivers the organic phase containing (2-bromoethyl)benzene, tetrabutyl ammonium chloride (PTC catalyst) in toluene; ISCO 2 delivers the aqueous phase containing sodium hydroxide in water. The total reactor volume would be 56 mL.

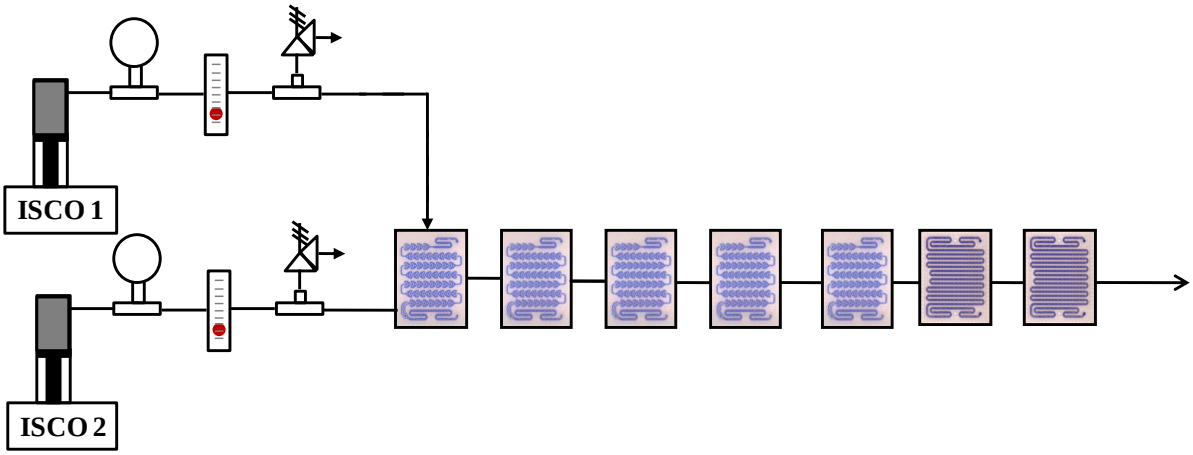


Figure 5.4 The continuous flow system configuration for PTC reactions.

5.3 Continuous Flow System

It will be beneficial to install a back-pressure regulator on our current system. The Corning® glass continuous flow reactor can withstand a considerable pressure over a wide temperature range (Figure 5.5 and Figure 5.6). Installing a back-pressure regulator would allow us to take advantage of this feature for gas-liquid reactions in the pharmaceutical and fine chemical industries.

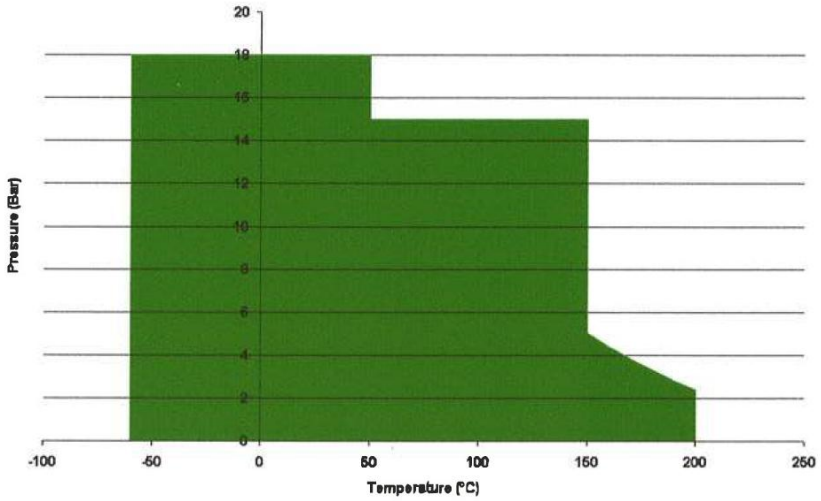


Figure 5.5 Temperature-pressure (^{o}C, Bar) boundary conditions for the reaction path.

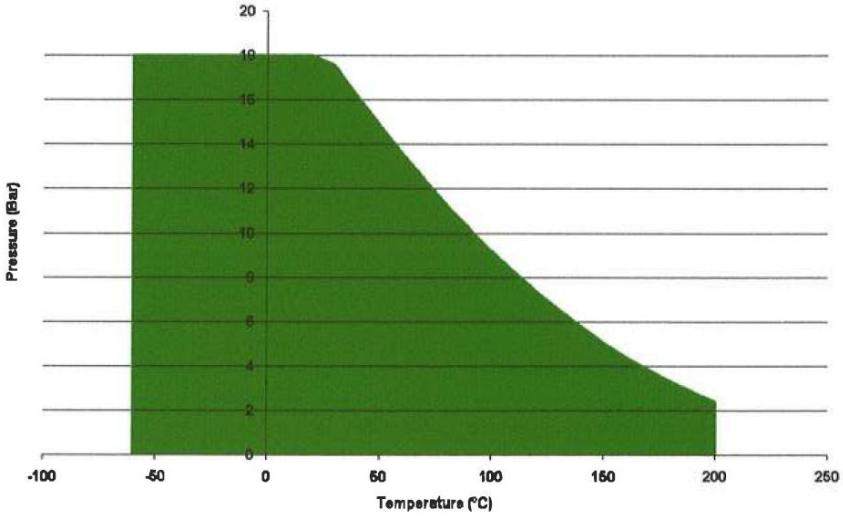


Figure 5.6 Temperature-pressure (^{o}C, Bar) boundary conditions for PFA tubing (inlet, outlet, and heat exchanger system).

APPENDIX A

BATCH EXPERIMENTAL PROCEDURE

Table A.1 Stock Solution Preparation for Batch Reactions.

Benzaldehyde Stock	
Reagent	**Amount**
Isopropanol, Anhydrous	30 mL
Benzaldehyde	2.5 mL

5 mol% $Al(OtBu)_3$ Stock	
Reagent	**Amount**
Toluene, Anhydrous	40 mL
$Al(OtBu)_3$	0.2669 g

Acetophenone Stock	
Reagent	**Amount**
Isopropanol, Anhydrous	3 mL
Acetophenone	30 mL

20 mol% $Al(OtBu)_3$	
Reagent	**Amount**
Toluene, Anhydrous	3 mL
$Al(OtBu)_3$	0.0810 g

Make stock solutions under inert atmosphere (Table A.1). Add 3 mL of the catalyst stock solutions to the carousel test tubes. Heat the reaction tubes with catalyst stock to the desired reaction temperature; wait for the temperature to stabilize. Add 2 mL of the reagent (benzaldehyde/acetophenone) stock solution to the reaction tubes at timed intervals. To quench the reaction, remove the reaction tube from the carousel and cool in an ice bath (test tube rack in ice bath on a stir plate) until cool to the touch, then add 2 mL of 2M HCl and let stir in ice bath for 5 min (Table A.2). Dilute the reaction mixture with 30mL of methanol. HPLC samples for the MPV reduction of benzaldehyde are made by adding 100 uL of the sample to 900uL of methanol in a GC vial. Acetophenone MPV reduction reactions require two different dilutions to make sure the peak areas of acetophenone and 1-phenylethanol are within the HPLC calibration curve ranges. HPLC

samples for the MPV reduction of acetophenone are made by adding 250 uL sample to 750 uL methanol and 750 uL sample to 250 uL methanol.

Table A.2 Example Batch Reaction Sampling Guide.

Reaction Tube	Start Time	Stop Time	Total Reaction Time	Dilution Time	Total Quench Time
1	0	36	36	41	5
2	1	34	33	39	5
3	2	32	30	37	5
4	3	30	27	35	5
5	4	28	24	33	5
6	5	26	21	31	5
7	6	24	18	29	5
8	7	22	15	27	5
9	8	20	12	25	5
10	9	18	9	23	5
11	10	16	6	21	5
12	11	14	3	19	5

APPENDIX B

CONTINUOUS FLOW EXPERIMENTAL PROCEDURE

Table B.1 Stock Solution Preparation for Continuous Flow Reactions.

Benzaldehyde Stock	
Reagent	**Amount**
Isopropanol, Anhydrous	500 mL
Benzaldehyde	43 mL
Dodecane	5.4 mL

5 mol% $Al(OtBu)_3$ Stock	
Reagent	**Amount**
Toluene, Anhydrous	600 mL
$Al(OtBu)_3$	3.8 g
Nonane	6 mL

20 mol% $Al(OtBu)_3$ Stock	
Reagent	**Amount**
Toluene, Anhydrous	600 mL
$Al(OtBu)_3$	15.5 g
Nonane	6 mL

Make stock solutions under inert atmosphere (Table B.1). Collect 1 mL stock solution samples for GC analysis ("cat stock", "BA stock") out of the flasks. Preheat the reactor to desired reaction temperature; wait for the temperature to stabilize. Use the filter when loading the catalyst stock solution into ISCO 2. Collect "0 sample" by disconnecting at the bottom of the flow meter in the ISCO 1 line. Dilute 0.5 mL of the "0 sample" with 20 mL of methanol and then make HPLC samples by adding 100 uL of the diluted sample to 900 uL methanol in a GC vial.

Wait two reactor volumes before collecting samples (system stabilized) and collect samples every reaction volume after that (Table B.2). The GC samples are made by adding 1 mL of the collected reaction mixture to a GC vial (no dilution). To quench the reaction, add 1mL of the collected reaction mixture to 1mL of cold methanol, let stir until cooled. Then add 0.4 mL of 2M HCl and let stir for 5 min. Dilute the quenched reaction mixture with an additional 15 mL of methanol. Make HPLC samples by adding 100uL of the diluted, quenched reaction mixture to 900 uL of methanol in a GC vial.

At the end of the experiment, rinse the ISCO pumps and reactor with isopropanol (ISCO 1) and toluene (ISCO 2), and cool the heat exchangers to room temperature.

Table B.2 Example Continuous Flow Sampling Guide.

80°C	**5 mL/min**	**2 and 3**	**Total Residence Volumes**	**Volume Used**	**Total Time (sec)**	**Total Time (Min)**	**Time of Volume (hr:min:sec)**	**TR 1 (°C)**	**TR 2 (°C)**	**TR 3 (°C)**	**P_{cat} (psi)**	**P_{BA} (psi)**	**RM_{Cat}**	**RM_{BA}**	**Total Flow Rate (ml/min)**
		Isco Fugi													
	BA Start Conc. Out of ISCO		0	0	0	0	0 : 00 : 00	------							
LAUDA Set Point=	86.8 C		1	56	672	11.20	0 : 11 : 12								
Thermo Set Point=	82.9 C		2	112	1344	22.40	0 : 22 : 24								
Vol. Cat=			3	168	2016	33.60	0 : 33 : 36								
Vol. BA=			4	224	2688	44.80	0 : 44 : 48								

80°C	**15 mL/min**	**6 and 9**	**Total Residence Volumes**	**Volume Used**	**Total Time (sec)**	**Total Time (Min)**	**Time of Volume (hr:min:sec)**	**TR 1 (°C)**	**TR 2 (°C)**	**TR 3 (°C)**	**P_{cat} (psi)**	**P_{BA} (psi)**	**RM_{Cat}**	**RM_{BA}**	**Total Flow Rate (ml/min)**
		Isco Fugi													
	BA Start Conc. Out of ISCO		0	0	0	0	0 : 00 : 00	------							
LAUDA Set Point=	86.8 C		1	56	224	3.73	0 : 3 : 44								
Thermo Set Point=	82.9 C		2	112	448	7.47	0 : 7 : 29								
Vol. Cat=			3	168	672	11.20	0 : 11 : 12								
Vol. BA=			4	224	896	14.93	0 : 14 : 56								

80°C	**30 mL/min**	**12 and 18**	**Total Residence Volumes**	**Volume Used**	**Total Time (sec)**	**Total Time (Min)**	**Time of Volume (hr:min:sec)**	**TR 1 (°C)**	**TR 2 (°C)**	**TR 3 (°C)**	**P_{cat} (psi)**	**P_{BA} (psi)**	**RM_{Cat}**	**RM_{BA}**	**Total Flow Rate (ml/min)**
		Isco Fugi													
	BA Start Conc. Out of ISCO		0	0	0	0	0 : 00 : 00	------							
LAUDA Set Point=	86.8 C		1	56	112	1.87	0 : 1 : 52								
Thermo Set Point=	82.9 C		2	112	224	3.73	0 : 3 : 44								
Vol. Cat=			3	168	336	5.60	0 : 5 : 36								
Vol. BA=			4	224	448	7.47	0 : 7 : 29								

APPENDIX C

PROPOSED MPV REDUCTION OF BENZAELDEHYDE MECHANISM

Figure C.1 shows the proposed mechanism for the MPV reduction of benzadehyde using $Al(OtBu)_3$, including the quench step.

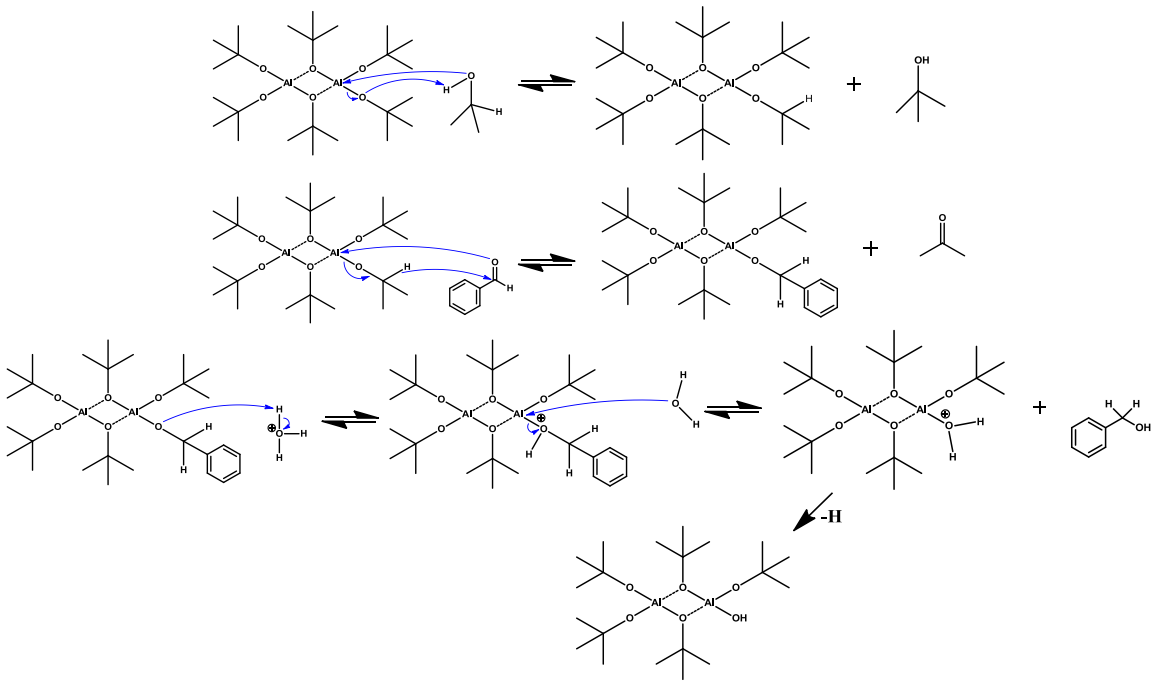


Figure C.1 Mechanism for the MPV reduction of benzaldehyde using $Al(OtBu)_3$.

APPENDIX D

^{1}H NMR DATA FOR AGGREGATION STATES OF CATALYSTS

Figure D.1 shows ^{1}H NMR for $Al(OtBu)_3$ in benzene and Figure D.2 shows the ^{1}H NMR for $Al(OiPr)_3$ in isopropanol. The rates of reaction between the two catalysts were attributed to their respective states of aggregation. The $Al(OtBu)_3$ catalysts exists as a cyclic dimer while the $Al(OiPr)_3$ catalyst exists as a tetrameric complex.[23] It has been previously suggested that only the non-bridging alkoxy groups can prefrom the hydrogen transfer required in the MPV reduction.[24] Comparing the number on non-bridging to bridging groups of the two catalyst complexes, we expect the cyclic dimer to be more reactive (2:1 vs. 1:1). This is consistent with our results.

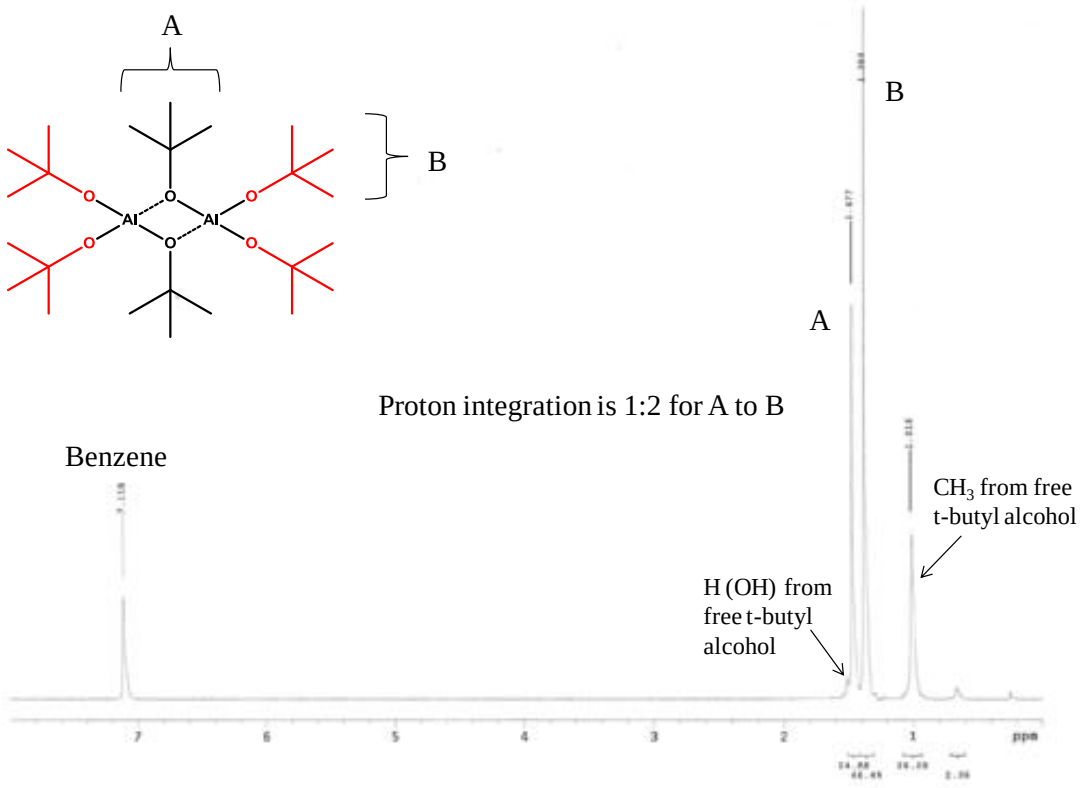


Figure D.1 ^{1}H NMR for $Al(OtBu)_3$ in benzene.

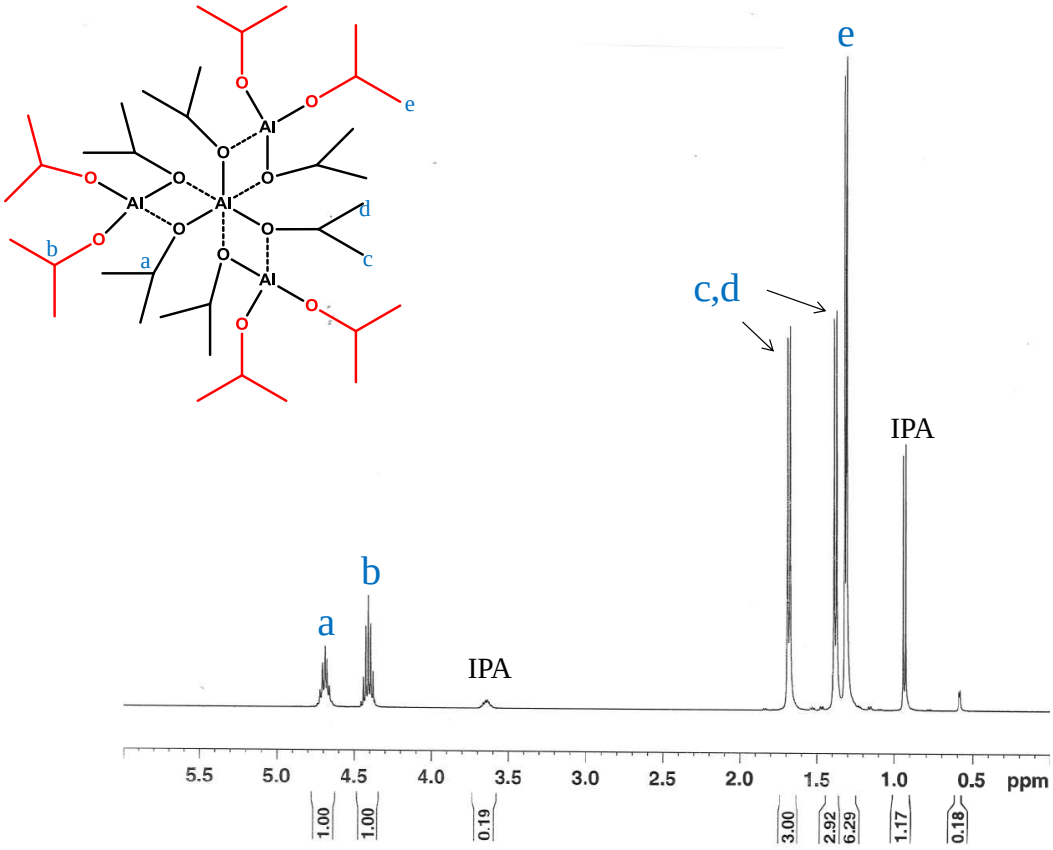


Figure D.2 **^{1}H NMR for Al(OiPr)$_3$ in isopropanol.**

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